Skeletal muscle development from hESC and its in vivo applications in animal models of muscular dystrophy

Grant Award Details

Skeletal muscle development from hESC and its in vivo applications in animal models of muscular dystrophy

Grant Type:	New Faculty I
Grant Number:	RN1-00525
Investigator:	**Name:** Tiziano Barberi **Institution:** City of Hope, Beckman Research Institute **Type:** PI
Disease Focus:	Muscular Dystrophy, Skeletal/Smooth Muscle disorders
Human Stem Cell Use:	Embryonic Stem Cell
Cell Line Generation:	Embryonic Stem Cell
Award Value:	$131,840
Status:	Closed

Grant Application Details

Application Title:	Skeletal muscle development from hESC and its in vivo applications in animal models of muscular dystrophy

Public Abstract:

Embryonic stem cells (ESC) originating from early stage embryos are able to differentiate into any type of cells in the body. The generation of ESC lines from human embryos (hESC) has attracted a lot of dispute among researchers, but raised the hope that one day hESCs can be used in cell replacement therapy for the treatment of degenerative diseases and cancer. Substantial efforts are currently focused on unveiling the full potential of hESCs by developing culture systems supporting the selective differentiation into the cell types of interest. We have reported the specific culture conditions that allow hESC differentiation in the originator cells (mesenchymal precursors) that form the bones, cartilage and muscles in our body. Furthermore, we then defined the conditions for selective generation of skeletal muscle cells from the hESC-derived mesenchymal precursors. Transplantation of these muscle cells into the limb muscle of immunodeficient mice showed their ability to survive and integrate in the host's tissue. Muscular dystrophies (MD) are a group of diseases affecting the muscles in our body. MD is characterized by progressive muscle weakness and atrophy for which there is no cure or treatment available. Based on our previous studies, we are proposing to optimize the culture conditions for the in vitro generation of skeletal muscle cells from hESCs and study the developmental mechanisms involved in this process. Furthermore, we will transplant these cells into dystrophic dogs, an animal model of MD, to evaluate their in vivo functionality and potential to repair or replace dystrophic muscle fibers. The accomplishment of our aims will contribute to the understanding of human skeletal muscle development and will provide the basis for the clinical application of hESC-derived cells in muscle diseases.

Statement of Benefit to California:

The establishment of pluripotent stem cell lines derived from the human blastocyst, hESC, opened a new era in biomedical research. Because of their embryonic origin, hESCs can be virtually differentiated in all the cells of all tissues in our body. There is great hope that in the near future hESC-derived specialized progeny will be used in cell-based therapy for a variety of degenerative diseases and cancer. The California stem-cell initiative, through CIRM, gives a significant boost to hESC research by funding pioneering projects in the field.

Muscular dystrophies (MD) are a group of > 20 genetic diseases characterized by progressive weakness and degeneration of the skeletal muscles that control movement. There are many forms of muscular dystrophy, some noticeable at birth (congenital muscular dystrophy) and others in adolescence (Becker and Duchenne MD). Duchenne MD is perhaps the most common form, with a worldwide incidence of 1 in 3,500 male births. This dystrophy occurs as the result of mutations in the gene that regulates dystrophin – a protein involved in maintaining the integrity of muscle fibers. Despite the substantial advances made in identifying the genetic defects causing these diseases, there is no treatment or cure available and affected children usually die in their teens. We propose to investigate the potential clinical applications of hESC-derived skeletal muscle cells upon transplantation in animal models of muscular dystrophy. In parallel, we propose to study the molecular basis of skeletal muscle development during hESC differentiation.

This research proposal will benefit the State of California and its citizens in the following ways. First of all, Californians are not immune to any form of MD and the overall incidence of this group of diseases is the same as elsewhere, with devastating consequences for the affected individuals and their families. We already showed that hESC-derived skeletal muscle cells can integrate and survive in a host muscle when transplanted in immunodeficient mice. Therefore, we expect that these cells will efficiently repair dystrophic muscle fibers in animal models of MD, such as dystrophic dogs. If our hypothesis proves to be correct, it is very likely that these cells will be used for transplantations in MD patients. Californians will then be the first to benefit from the outcome of the proposed research. In addition, a successful ESC-based therapy of MD will certainly encourage and stimulate research for other ESC-based therapies for related diseases.

In conclusion, the CIRM initiative will undoubtedly lead to the discovery of a therapy and/or the developmental mechanisms leading to some disease. That in itself will put California at the top of ESC research with enormous benefits for all Californians.

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